Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Progressive Multifocal Leukoencephalopathy/JC Virus Infection

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Epidemiology

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS), caused by the polyoma virus JC virus (JCV) and characterized by focal demyelination.[1,2] The virus has worldwide distribution, with a seroprevalence of 39% to 69% among adults.[3-6] Primary JCV infection usually occurs in childhood, without identified symptoms, and establishes a chronic asymptomatic carrier state in most individuals, which explains the detection of viral DNA in urine in 20% to 30% of adults who are immunologically normal.[4,7-11]

Outside the context of HIV infection, PML is rare and characteristically manifests as a complication of other immunocompromising diseases or therapies.[12-14] In recent years, PML has been reported in patients treated with immunomodulatory humanized antibodies, including natalizumab,[15] efalizumab,[16] infliximab,[17] and rituximab.[18] Concern has been raised about a possible increased risk of PML in HIV-infected patients treated with rituximab for non-Hodgkin lymphoma,[19,20] but no reports have yet documented PML in that setting.

Before the advent of combination antiretroviral therapy (ART), PML developed in 3% to 7% of patients with AIDS[21-23] and was almost invariably fatal; spontaneous remissions were rare.[24] With the widespread use of ART in the developed world, incidence of PML has decreased substantially,[25] whereas mortality in HIV-infected persons who develop the disease has remained high.[26-28] Unlike some of the other CNS opportunistic infections that are almost wholly prevented when CD4 T-lymphocyte (CD4 cell) counts are maintained above 100 to 200 cells/mm^3, PML can still appear in such patients and in those on ART.[2,29,30] Moreover, PML can develop in the setting of initiating ART and immune reconstitution, discussed below.[2,31]

Clinical Manifestations

PML manifests as focal neurological deficits, usually with insidious onset and steady progression. Because the demyelinating lesions can involve different brain regions, specific deficits vary from patient to patient. Any region of the CNS can be involved, although some areas seem to be more favored, including the occipital lobes (with hemianopsia), frontal and parietal lobes (aphasia, hemiparesis, and hemisensory deficits), and cerebellar peduncles and deep white matter (dysmetria and ataxia).[12] Spinal cord involvement is rare.[32] Although lesions can be multiple, one often is clinically predominant. Initial symptoms and signs often begin as partial deficits (e.g., weakness in one leg) that worsen over time and involve a larger territory (e.g., evolution to hemiparesis) as individual lesions expand concentrically or along white matter tracts. The focal or multifocal nature of the pathology is responsible for the consistency of clinical presentations with distinct focal symptoms and signs, rather than as a more diffuse encephalopathy, or isolated dementia or behavioral syndrome, all of which are uncommon without concomitant focal findings.[33]

The time course of this evolving demyelination, with clinical progression over several weeks, often provides a clue to diagnosis because the other major opportunistic focal brain disorders (cerebral toxoplasmosis and primary CNS lymphoma) characteristically progress in hours to days and cerebral infarcts begin even more abruptly. Headache and fever are not characteristic of the disease, except in severe cases of inflammatory PML (see below), but seizures develop in nearly 20% of PML patients and are associated with lesions immediately adjacent to the cortex.[34]

Diagnosis

Initial recognition of PML relies on a combination of clinical and neuroimaging findings. The first step is usually identifying the clinical picture of steady progression of focal neurological deficits. Magnetic resonance imaging (MRI) almost always confirms distinct white matter lesions in areas of the brain corresponding to the

clinical deficits. The lesions are hyperintense (white) on T2-weighted and fluid attenuated inversion recovery sequences and hypointense (dark) on T1-weighted sequences.[2] The latter characteristic, though possibly subtle, helps to distinguish the PML lesion from other pathologies, including the white matter lesions of HIV encephalitis. In contrast to cerebral toxoplasmosis and primary CNS lymphoma, no mass effect or displacement of normal structures is usually evident. Although contrast enhancement is present in 10% to 15% of cases, it is usually sparse, with a thin or reticulated appearance adjacent to the edge of the lesions. Exceptions to these characteristic imaging findings can occur when the inflammatory form of PML develops in the setting of immune reconstitution after initiation of ART (see below). Advanced neuroimaging techniques, such as diffusion-weighted imaging and magenetic resonance (MR) spectroscopy, may provide additional diagnostic information.[35-37] New PML lesions and the advancing edge of large lesions have high signal on diffusion-weighted imaging and normal-to-low apparent diffusion coefficient signifying restricted diffusion. These changes relate to regions of active infection and oligodendrocyte swelling. Older lesions and the centers of larger lesions have increased apparent diffusion coefficient values. MR spectroscopy typically shows decreased N-acetylaspartate and increased choline, related to axonal loss and cell membrane and myelin breakdown, respectively, with the greatest changes at the center of lesions.[38]

In most cases of PML, the combined clinical and radiographic presentations support a presumptive diagnosis. Confirming the diagnosis, however, is invaluable. Certainly for atypical cases but even for typical cases, confirmation allows physicians to initiate ART rapidly and with certainty and prevents the need to revisit diagnosis when disease progression continues. Confirmed diagnosis also informs discussions of prognosis.

The usual first step in confirming the diagnosis is to test cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) for the presence of JCV DNA. The assay is positive in approximately 70% to 90% of patients not taking ART, for whom a positive result can be considered diagnostic in the appropriate clinical context, that is, those with subacute onset of focal neurological abnormalities and suggestive imaging findings.[9,39] JCV may be detectable in the CSF of as few as 60% of ART-treated patients.[40] In patients not taking ART, the number of JCV DNA copies can add additional information for prognosis, although the relationship between copy number and prognosis is less clear in patients taking ART.[41,42] CSF analysis can be repeated if JCV PCR is negative yet suspicion of PML remains high and alternative diagnoses have been excluded (e.g., by PCR analyses of CSF for varicella zoster virus and Epstein-Barr virus for varicella zoster virus encephalitis and primary CNS lymphoma, respectively).

In some instances, brain biopsy is required to establish the diagnosis. PML can usually be identified by the characteristic tissue cytopathology, including oligodendrocytes with intranuclear inclusions, bizarre astrocytes, and lipid-laden macrophages, with identification of JCV or cross reacting polyoma virus by immunohistochemistry, *in situ* nucleic acid hybridization, or electron microscopy.[12,43,44]

Serologic testing generally is not useful because of high anti-JCV seroprevalence in the general population. Recently, however, antibody testing has been assessed for stratifying risk of PML with natalizumab treatment[6] and it eventually may be applied to risk in HIV. Detection of intrathecally produced anti-JCV antibodies may prove useful for diagnostic testing[45] but requires further prospective study.

Preventing Exposure

JCV has a worldwide distribution and, as previously noted, 20% to 60% of people exhibit serologic evidence of exposure by their late teens.[46] Currently, there is no known way to prevent exposure to the virus.

Preventing Disease

In many individuals, JCV likely continues as a latent and intermittently productive, although clinically silent, infection in the kidney or other systemic sites, and systemic infection may increase in the presence of immunosuppression. Whether JCV is also latent in the CNS or PML results from temporally more proximate hematogenous dissemination is the subject of debate.[47,48] Protection is conferred by either preventing spread to

the CNS or by preventing active viral replication with effective immunosurveillance. Therefore, the only effective way to prevent disease is to prevent progression of HIV-related immunosuppression with ART **(AII)**.

Treating Disease

No specific therapy exists for JCV infection or PML. The main approach to treatment involves ART to reverse the immunosuppression that interferes with the normal host response to this virus. Treatment strategies depend on the patient's antiretroviral (ARV) treatment status and its effect. Thus, in patients with PML who are not on therapy, ART should be started immediately **(AII)**. In this setting, approximately half of HIV-infected PML patients experience a remission in which disease progression stops. Neurological deficits often persist, but some patients experience clinical improvement.[27,49-55] In one retrospective study of 118 consecutive patients with PML who received ART, 75 patients (63.6%) survived for a median of 114 weeks (2.2 years) after diagnosis of PML.[55] Neurological function in the survivors was categorized as cure or improvement in 33, stabilization or worsening in 40, and unknown in 2. Another recent retrospective case series reported that 42% of PML survivors on ART had moderate-to-severe disability.[56] Peripheral blood CD4 cell count at presentation was the only variable that predicted survival; the odds ratio for death was 2.7 among patients with CD4 counts <100 cells/mm^3 compared with patients who had higher CD4 cell counts. In other case series, worse prognosis was also associated with high plasma HIV RNA levels at the time of presentation, poor virologic responses to ART, and the presence of lesions in the brain stem.[30,49,51,52,54,55,57] Contrast enhancement on imaging may predict better outcome.[29]

ART should be optimized for virologic suppression in patients with PML who have received ART but remain HIV viremic because of inadequate adherence or ARV resistance **(AIII)**. More problematic are patients who develop PML despite successful virologic suppression while taking ART. A preliminary report of PML patients treated intensively with four classes of ART (including enfuvirtide) suggested that the strategy might offer higher than anticipated survival,[58] but it has not yet been followed by a full report or structured trial. Therefore, there is no evidence supporting ART intensification for PML.

The use of ARV drugs that better penetrate the CNS also has been proposed, with use of the CNS Penetration Effectiveness (CPE) score of drug regimens as a guide. This score is based on the pharmacology of ARV drugs with respect to their entry into the CNS (or, more often, the CSF) and, where available, on their CNS anti-HIV effects.[59] One report found that at the beginning of the combination ART era, a high CPE score was associated with longer survival after a PML diagnosis, whereas in the late, more recent ART period, the effect of the CPE score disappeared as more potent ARV regimens led to more effective plasma viral load control.[60] Hence, in the current era, the effectiveness of selecting a treatment regimen with a high CPE score is not established. It seems likely that systemic rather than CNS efficacy is the salient aspect of ART in this setting because ART's most important effect on PML may be restoration of effective anti-JCV immunity that can limit CNS infection.

The history of more specifically targeted treatments for PML includes many anecdotal reports of success that have not been confirmed by controlled studies. Based on case reports and demonstration of *in vitro* inhibitory activity against JCV, intravenous (IV) and intrathecal cytarabine (cytosine arabinoside) were tested in a clinical trial, but neither demonstrated clinical benefit.[61] Therefore, treatment with cytarabine is **not recommended (AII)**. Similarly, cidofovir initially was reported to have a salutary clinical effect, but several large studies—including retrospective case-control studies, an open-label clinical trial, and a meta-analysis that included patients from five large studies—demonstrated no benefit.[40,53-55,62] Thus, treatment with cidofovir is also **not recommended (AII)**. A lipid-ester derivative, hexadecyloxypropyl-cidofovir, recently has been reported to suppress JCV replication in cell culture,[63] but its efficacy in HIV-associated PML is unknown.

On the basis of a report indicating that the serotonergic 5HT2a receptor can serve as a cellular receptor for JCV in a glial cell culture system,[64,65] drugs that block the 5HT2a receptor, including olanzapine, zisprasidone, mirtazapine, cyproheptadine, and risperidone, have been suggested as treatment for PML,[66]

although the rationale for this practice has been questioned.[67] Again, anecdotes about favorable outcomes[1,68-71] have not been substantiated by reports of genuine benefit in larger case series, cohort studies, or formal clinical trials. Thus, at this time, this class of drugs **cannot be recommended (BIII)**.

After a cell-culture study indicated that JCV replication could be inhibited by a topoisomerase inhibitor,[72] an analogue, topotecan, was studied in a small trial. Results suggested a salutary effect in some patients, although the outcome likely was little different from the natural course in other patients with AIDS, and the main toxicities were hematologic.[73] At this time, topotecan also is **not recommended (BIII)**.

A Phase I/II clinical trial of the antimalarial drug mefloquine recently was initiated based on its demonstrated *in vitro* anti-JCV activity. The trial was later halted by the sponsoring pharmaceutical company, however, because of lack of demonstrable efficacy (http://clinicaltrials.gov/ct2/show/NCT00746941). To date, the results have only been presented at a meeting and in abstract.[74]

Immunomodulatory approaches to the treatment of PML in HIV-infected patients also have been tried, but none has yet been studied in a prospective, controlled clinical trial. Although an initial retrospective analysis suggested that interferon-alpha might improve survival,[75] a subsequent retrospective analysis did not demonstrate benefit beyond that afforded by ART; therefore, interferon-alpha **cannot be recommended**.[76] A single report described failure of interferon-beta treatment of HIV-associated PML[77] and natalizumab-related PML developed in patients given interferon-beta for multiple sclerosis.[15] Case reports have described improvement or recovery in PML-related neurological dysfunction in three patients who were not HIV infected: one with Hodgkin lymphoma treated with autologous bone marrow transplantation, one with low-grade lymphoma and allogeneic stem cell transplantation, and one with myelodysplastic syndrome treated with interleukin-2.[78-80] Like the other reports, these, too, have not been followed up with more substantial trials.

Special Considerations with Regard to Starting ART

ART should be started in patients not on HIV treatment as soon as PML is recognized **(AII)**. For patients already on treatment who have demonstrated plasma viremia and are adherent to therapy, ART should be adjusted based on plasma virus susceptibility **(AII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Treatment response should be monitored with clinical examination and MRI. In patients with detectable JCV DNA in their CSF before initiation of ARV treatment, quantitation of CSF JCV DNA may prove useful as an index to follow for assessing treatment response. No clear guidelines exist for the timing of follow-up assessments, but it is reasonable to be guided by clinical progress. In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation to screen for radiographic signs of progression or of immune response, and can serve as a further baseline for subsequent scans should the patient begin to deteriorate. In patients who clinically worsen before or after this 6- to 8-week period, repeat neuroimaging should be obtained as soon as worsening is recognized **(BIII)**.

PML-Immune Reconstitution Inflammatory Syndrome

PML has been reported to occur within the first weeks to months after initiating ART[2,30,31,81,82] with clinical and radiographic features that differ from classical PML, including lesions with contrast enhancement, edema and mass effect, and a more rapid clinical course. This presentation has been referred to as inflammatory PML or PML-immune reconstitution inflammatory syndrome (PML-IRIS). Both unmasking of cryptic PML and paradoxical worsening in a patient with an established PML diagnosis have been observed. Histopathology typically demonstrates perivascular mononuclear inflammatory infiltration.[83-86] Further study is needed to determine whether the likelihood of detecting JCV in CSF is different in patients who have PML-IRIS than in those with classical PML.[49,87] Unmasked PML-IRIS is presumed to represent the effects of a restored immune response to JCV infection in the context of ART, with resultant local immune and inflammatory responses, but other undefined factors also may contribute to unmasked PML-IRIS. A similar,

though often more fulminant, form of PML-IRIS has been reported after discontinuation of natalizumab and plasma exchange in patients with multiple sclerosis who develop PML.[15,88,89]

Because ART-induced immune reconstitution may be associated with both onset and paradoxical worsening of PML, corticosteroids have been used empirically in this setting, with reported benefit.[2,82] Further study of corticosteroids for PML is needed to confirm efficacy and refine dosage and duration. At present, however, use of the drugs appears justified for PML-IRIS characterized by contrast enhancement, edema or mass effect, and clinical deterioration **(BIII)**. The decision to use steroids can be difficult because it is the immune response to JCV that controls the infection and treatments that blunt that response can be deleterious. Nevertheless, the inflammatory response against PML can, at times, be more damaging than the virus itself, and corticosteroids likely have a role in treatment of these patients.

The dosage and duration of corticosteroids for PML-IRIS have not been established. In the absence of comparative data, adjuvant corticosteroid therapy should be tailored to individual patients. One approach, modeled on treatment of multiple sclerosis flairs, is to begin with a 3- to 5 day course of IV methylprednisolone dosed at 1 g per day, followed by an oral prednisone taper, dosed according to clinical response. A taper may begin with a dose of 60 mg per day in a single dose, tapered over 1 to 6 weeks. Clinical status should be monitored carefully during this taper in an attempt to minimize systemic and immune effects while avoiding IRIS recrudescence. Contrast-enhanced MRI at 2 to 6 weeks may be helpful in documenting resolution of inflammation and edema and to obtain a new baseline, recognizing that the MRI appearance may worsen despite clinical improvement and that clinical status is likely the best indicator of treatment efficacy. Importantly, ART should be continued at the standard therapeutic doses during this period **(AIII)**.

A single case report suggested that maraviroc might be beneficial for PML-IRIS,[90] presumably related to the immunomodulatory rather than ARV properties of the CCR5 inhibitor. However, it has not yet been followed by further studies.

Although some clinicians may want to use adjuvant corticosteroid therapy to treat all cases of PML regardless of whether there is evidence of IRIS, this action is not justified and should be discouraged in patients who have no evidence of substantial inflammation on contrast-enhanced neuroimaging or on pathological examination **(CIII)**. In patients whose condition worsens, imaging can be repeated to monitor for development of IRIS before initiating corticosteroids.

Managing Treatment Failure

Because PML remission can take several weeks, no strict criteria define treatment failure. However, a working definition may be continued clinical worsening and continued detection of CSF JCV without substantial decrease within 3 months. In the case of ART, plasma HIV RNA levels and blood CD4 cell count responses provide ancillary predictive information. Failing ART regimens should be changed based on standard guidelines for use of ART. When PML continues to worsen despite suppressive anti-HIV treatment, one of the unproven therapies described above can be considered, although the possibility of toxicity must be balanced against the unproven benefits of these treatments. Better treatments and rigorous assessment of them are needed.

Preventing Recurrence

Patients who experience remission of PML after ART rarely suffer subsequent recrudescence.[53] The main preventive measure, based on its role in reversing the disease, is treatment with an effective ART regimen that suppresses viremia and maintains CD4 cell counts **(AII)**.

Special Considerations During Pregnancy

Diagnostic evaluation of PML should be the same in pregnant women as in women who are not pregnant. Therapy during pregnancy should consist of initiating or optimizing the ARV regimen.

Recommendations for Preventing and Treating PML and JCV

- There is no effective antiviral therapy for preventing or treating JCV infections or PML.
- The main approach to treatment is to preserve immune function or reverse HIV-associated immunosuppression with effective ART.
- In ART-naive patients who are diagnosed with PML, ART should be started immediately **(AII)**.
- In patients who are receiving ART but remains viremic because of inadequate adherence or drug resistance, ART should be optimized to achieve HIV suppression **(AIII)**.

Key to Acronyms: ART = antiretroviral therapy; JCV = JC virus; PML = progressive multifocal leukoencephalopathy.

References

1. Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: Has the disease outgrown its name? *Ann Neurol*. Aug 2006;60(2):162-173. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16862584.
2. Cinque P, Koralnik IJ, Gerevini S, Miro JM, Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. *Lancet Infect Dis*. Oct 2009;9(10):625-636. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19778765.
3. Kean JM, Rao S, Wang M, Garcea RL. Seroepidemiology of human polyomaviruses. *PLoS Pathog*. Mar 2009;5(3):e1000363. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19325891.
4. Egli A, Infanti L, Dumoulin A, et al. Prevalence of Polyomavirus BK and JC Infection and Replication in 400 Healthy Blood Donors. *J Infect Dis*. Jan 27 2009. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19199540.
5. Antonsson A, Green AC, Mallitt KA, et al. Prevalence and stability of antibodies to the BK and JC polyomaviruses: a long-term longitudinal study of Australians. *J Gen Virol*. Jul 2010;91(Pt 7):1849-1853. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20219899.
6. Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Annals of neurology*. Sep 2010;68(3):295-303. Available at http://www.ncbi.nlm.nih.gov/pubmed/20737510.
7. Kitamura T, Aso Y, Kuniyoshi N, Hara K, Yogo Y. High incidence of urinary JC virus excretion in nonimmunosuppressed older patients. *J Infect Dis*. Jun 1990;161(6):1128-1133. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2161040.
8. Sundsfjord A, Flaegstad T, Flo R, et al. BK and JC viruses in human immunodeficiency virus type 1-infected persons: prevalence, excretion, viremia, and viral regulatory regions. *J Infect Dis*. Mar 1994;169(3):485-490. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8158020.
9. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. Jan 15 1999;52(2):253-260. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9932940.
10. Lednicky JA, Vilchez RA, Keitel WA, et al. Polyomavirus JCV excretion and genotype analysis in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. Apr 11 2003;17(6):801-807. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12660526.
11. Kato A, Kitamura T, Takasaka T, et al. Detection of the archetypal regulatory region of JC virus from the tonsil tissue of patients with tonsillitis and tonsilar hypertrophy. *J Neurovirol*. Aug 2004;10(4):244-249. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15371154.
12. Richardson EP, Jr., Webster HD. Progressive multifocal leukoencephalopathy: its pathological features. *Prog Clin Biol Res*. 1983;105:191-203. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6304757.
13. Garcia-Suarez J, de Miguel D, Krsnik I, Banas H, Arribas I, Burgaleta C. Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. *Am J*

Hematol. Dec 2005;80(4):271-281. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16315252.

14. Amend KL, Turnbull B, Foskett N, Napalkov P, Kurth T, Seeger J. Incidence of progressive multifocal leukoencephalopathy in patients without HIV. *Neurology*. Oct 12 2010;75(15):1326-1332. Available at http://www.ncbi.nlm.nih.gov/pubmed/20938025.
15. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol*. Apr 2010;9(4):438-446. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20298967.
16. Molloy ES, Calabrese LH. Therapy: Targeted but not trouble-free: efalizumab and PML. *Nat Rev Rheumatol*. Aug 2009;5(8):418-419. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19648939.
17. Kumar D, Bouldin TW, Berger RG. A case of progressive multifocal leukoencephalopathy in a patient treated with infliximab. *Arthritis and rheumatism*. Nov 2010;62(11):3191-3195. Available at http://www.ncbi.nlm.nih.gov/pubmed/20722036.
18. Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. *Lancet Oncol*. Aug 2009;10(8):816-824. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19647202.
19. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol*. Sep 1 2006;24(25):4123-4128. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16896005.
20. Mounier N, Spina M, Gisselbrecht C. Modern management of non-Hodgkin lymphoma in HIV-infected patients. *Br J Haematol*. Mar 2007;136(5):685-698. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17229246.
21. Petito CK, Cho ES, Lemann W, Navia BA, Price RW. Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. *J Neuropathol Exp Neurol*. Nov 1986;45(6):635-646. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3021914.
22. Anders KH, Guerra WF, Tomiyasu U, Verity MA, Vinters HV. The neuropathology of AIDS. UCLA experience and review. *Am J Pathol*. Sep 1986;124(3):537-558. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2876640.
23. Lang W, Miklossy J, Deruaz JP, et al. Neuropathology of the acquired immune deficiency syndrome (AIDS): a report of 135 consecutive autopsy cases from Switzerland. *Acta Neuropathol (Berl)*. 1989;77(4):379-390. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2540610.
24. Berger JR, Mucke L. Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. *Neurology*. Jul 1988;38(7):1060-1065. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3386823.
25. d'Arminio Monforte A, Cinque P, Mocroft A, et al. Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Annals of neurology*. Mar 2004;55(3):320-328. Available at http://www.ncbi.nlm.nih.gov/pubmed/14991809.
26. Mocroft A, Collaboration AC. OIs, AIDS-Defining Conditions, and HIV-1 Disease Burden. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 27, 2007, 2007; Los Angeles.
27. Dworkin MS, Wan PC, Hanson DL, Jones JL. Progressive multifocal leukoencephalopathy: improved survival of human immunodeficiency virus-infected patients in the protease inhibitor era. *J Infect Dis*. Sep 1999;180(3):621-625. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10438348.
28. Garvey L, Winston A, Walsh J, et al. HIV-associated central nervous system diseases in the recent combination antiretroviral therapy era. *Eur J Neurol*. Mar 2011;18(3):527-534. Available at http://www.ncbi.nlm.nih.gov/pubmed/21159073.
29. Berger JR, Levy RM, Flomenhoft D, Dobbs M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. *Ann Neurol*. Sep 1998;44(3):341-349. Available at

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9749600.

30. Cinque P, Bossolasco S, Brambilla AM, et al. The effect of highly active antiretroviral therapy-induced immune reconstitution on development and outcome of progressive multifocal leukoencephalopathy: study of 43 cases with review of the literature. *J Neurovirol*. 2003;9 Suppl 1:73-80. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12709876.
31. Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? *J Neurovirol*. 2003;9 Suppl 1:25-31. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12709868.
32. Bernal-Cano F, Joseph JT, Koralnik IJ. Spinal cord lesions of progressive multifocal leukoencephalopathy in an acquired immunodeficiency syndrome patient. *Journal of neurovirology*. Oct 2007;13(5):474-476. Available at http://www.ncbi.nlm.nih.gov/pubmed/17994433.
33. Zunt JR, Tu RK, Anderson DM, Copass MC, Marra CM. Progressive multifocal leukoencephalopathy presenting as human immunodeficiency virus type 1 (HIV)-associated dementia. *Neurology*. Jul 1997;49(1):263-265. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9222204.
34. Lima MA, Drislane FW, Koralnik IJ. Seizures and their outcome in progressive multifocal leukoencephalopathy. *Neurology*. Jan 24 2006;66(2):262-264. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16434670.
35. Chang L, Ernst T, Tornatore C, et al. Metabolite abnormalities in progressive multifocal leukoencephalopathy by proton magnetic resonance spectroscopy. *Neurology*. Apr 1997;48(4):836-845. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9109865.
36. Mader I, Herrlinger U, Klose U, Schmidt F, Kuker W. Progressive multifocal leukoencephalopathy: analysis of lesion development with diffusion-weighted MRI. *Neuroradiology*. Oct 2003;45(10):717-721. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12942223.
37. da Pozzo S, Manara R, Tonello S, Carollo C. Conventional and diffusion-weighted MRI in progressive multifocal leukoencephalopathy: new elements for identification and follow-up. *Radiol Med*. Oct 2006;111(7):971-977. Available at http://www.ncbi.nlm.nih.gov/pubmed/17021685.
38. Shah R, Bag AK, Chapman PR, Cure JK. Imaging manifestations of progressive multifocal leukoencephalopathy. *Clin Radiol*. Jun 2010;65(6):431-439. Available at http://www.ncbi.nlm.nih.gov/pubmed/20451009.
39. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS*. Jan 1997;11(1):1-17. Available at http://www.ncbi.nlm.nih.gov/pubmed/9110070.
40. De Luca A, Ammassari A, Pezzotti P, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. *AIDS*. Sep 12 2008;22(14):1759-1767. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18753934.
41. Yiannoutsos CT, Major EO, Curfman B, et al. Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leukoencephalopathy. *Annals of neurology*. Jun 1999;45(6):816-821. Available at http://www.ncbi.nlm.nih.gov/pubmed/10360779.
42. Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis*. Mar 1 2005;40(5):738-744. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15714422.
43. Silver SA, Arthur RR, Erozan YS, Sherman ME, McArthur JC, Uematsu S. Diagnosis of progressive multifocal leukoencephalopathy by stereotactic brain biopsy utilizing immunohistochemistry and the polymerase chain reaction. *Acta Cytol*. Jan-Feb 1995;39(1):35-44. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7847007.
44. Jochum W, Weber T, Frye S, Hunsmann G, Luke W, Aguzzi A. Detection of JC virus by anti-VP1 immunohistochemistry in brains with progressive multifocal leukoencephalopathy. *Acta Neuropathol (Berl)*. Sep 1997;94(3):226-231. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9292691.

45. Knowles WA, Luxton RW, Hand JF, Gardner SD, Brown DW. The JC virus antibody response in serum and cerebrospinal fluid in progressive multifocal leucoencephalopathy. *Clin Diagn Virol*. Aug 1995;4(2):183-194. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15566839.

46. Knowles WA. Discovery and epidemiology of the human polyomaviruses BK virus (BKV) and JC virus (JCV). *Adv Exp Med Biol*. 2006;577:19-45. Available at http://www.ncbi.nlm.nih.gov/pubmed/16626025.

47. Perez-Liz G, Del Valle L, Gentilella A, Croul S, Khalili K. Detection of JC virus DNA fragments but not proteins in normal brain tissue. *Ann Neurol*. Aug 7 2008. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18688812.

48. Tan CS, Ellis LC, Wuthrich C, et al. JC virus latency in the brain and extraneural organs of patients with and without progressive multifocal leukoencephalopathy. *J Virol*. Sep 2010;84(18):9200-9209. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20610709.

49. Antinori A, Cingolani A, Lorenzini P, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol*. 2003;9 Suppl 1:47-53. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12709872.

50. Clifford DB, Yiannoutsos C, Glicksman M, et al. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology*. Feb 1999;52(3):623-625. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10025799.

51. Gasnault J, Taoufik Y, Goujard C, et al. Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy. *J Neurovirol*. Aug 1999;5(4):421-429. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10463864.

52. Tassie JM, Gasnault J, Bentata M, et al. Survival improvement of AIDS-related progressive multifocal leukoencephalopathy in the era of protease inhibitors. Clinical Epidemiology Group. French Hospital Database on HIV. *AIDS*. Oct 1 1999;13(14):1881-1887. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10513646.

53. Cinque P, Pierotti C, Vigano MG, et al. The good and evil of HAART in HIV-related progressive multifocal leukoencephalopathy. *Journal of neurovirology*. Aug 2001;7(4):358-363. Available at http://www.ncbi.nlm.nih.gov/pubmed/11517417.

54. Marra CM, Rajicic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS*. Sep 6 2002;16(13):1791-1797. Available at http://www.ncbi.nlm.nih.gov/pubmed/12218391.

55. Berenguer J, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. *Clin Infect Dis*. Apr 15 2003;36(8):1047-1052. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12684918.

56. Lima MA, Bernal-Cano F, Clifford DB, Gandhi RT, Koralnik IJ. Clinical outcome of long-term survivors of progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry*. Aug 14 2010. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20710013.

57. Pazzi A, Galli L, Costenaro P, et al. The Relationship between Outcome of Progressive Multifocal Leukoencephalopathy and Type and Response to ART in Previously HAART-untreated Patients. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007, 2007; Los Angeles.

58. Gasnault J, Hendel Chavez E, Dorofeev E, et al. Acceleration of immune recovery on intensified ART improves survival in patients with AIDS-related PML : preliminary reports of the ANRS 125 Trial. Paper presented at: CROI 20072007; Los Angeles, CA.

59. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. Jan 2008;65(1):65-70. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18195140.

60. Lanoy E, Guiguet M, Bentata M, et al. Survival after neuroAIDS: association with antiretroviral CNS Penetration-Effectiveness score. *Neurology*. Feb 15 2011;76(7):644-651. Available at http://www.ncbi.nlm.nih.gov/pubmed/21248274.

61. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. *N Engl J Med*. May 7 1998;338(19):1345-1351. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9571254.

62. Gasnault J, Kousignian P, Kahraman M, et al. Cidofovir in AIDS-associated progressive multifocal leukoencephalopathy: a monocenter observational study with clinical and JC virus load monitoring. *J Neurovirol*. Aug 2001;7(4):375-381. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11517420.

63. Jiang ZG, Cohen J, Marshall LJ, Major EO. Hexadecyloxypropyl-cidofovir (CMX001) suppresses JC virus replication in human fetal brain SVG cell cultures. *Antimicrob Agents Chemother*. Nov 2010;54(11):4723-4732. Available at http://www.ncbi.nlm.nih.gov/pubmed/20823288.

64. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science*. Nov 19 2004;306(5700):1380-1383. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15550673.

65. O'Hara BA, Atwood WJ. Interferon beta1-a and selective anti-5HT(2a) receptor antagonists inhibit infection of human glial cells by JC virus. *Virus Res*. Mar 2008;132(1-2):97-103. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18093678.

66. Altschuler EL, Kast RE. The atypical antipsychotic agents ziprasidone [correction of zisprasidone], risperdone and olanzapine as treatment for and prophylaxis against progressive multifocal leukoencephalopathy. *Med Hypotheses*. 2005;65(3):585-586. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16004936.

67. Santagata S, Kinney HC. Mechanism of JCV entry into oligodendrocytes. *Science*. Jul 15 2005;309(5733):381-382. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16020715.

68. Focosi D, Fazzi R, Montanaro D, Emdin M, Petrini M. Progressive multifocal leukoencephalopathy in a haploidentical stem cell transplant recipient: A clinical, neuroradiological and virological response after treatment with risperidone. *Antiviral Res*. Nov 27 2006. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17140673.

69. Vulliemoz S, Lurati-Ruiz F, Borruat FX, et al. Favourable outcome of progressive multifocal leucoencephalopathy in two patients with dermatomyositis. *J Neurol Neurosurg Psychiatry*. Sep 2006;77(9):1079-1082. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16914758.

70. Lanzafame M, Ferrari S, Lattuada E, et al. Mirtazapine in an HIV-1 infected patient with progressive multifocal leukoencephalopathy. *Infez Med*. Mar 2009;17(1):35-37. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19359824.

71. Cettomai D, McArthur JC. Mirtazapine use in human immunodeficiency virus-infected patients with progressive multifocal leukoencephalopathy. *Arch Neurol*. Feb 2009;66(2):255-258. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19204164.

72. Kerr DA, Chang CF, Gordon J, Bjornsti MA, Khalili K. Inhibition of human neurotropic virus (JCV) DNA replication in glial cells by camptothecin. *Virology*. Oct 1993;196(2):612-618. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8396804.

73. Royal W, 3rd, Dupont B, McGuire D, et al. Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. *J Neurovirol*. Jun 2003;9(3):411-419. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12775425.

74. Clifford D, Nath A, Cinque P, et al. Mefloquine Treatment in Patients with Progressive Multifocal Leukoencephalopathy. *Neurology*. 2011;76:A28.

75. Huang SS, Skolasky RL, Dal Pan GJ, Royal W, 3rd, McArthur JC. Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol*. Jun 1998;4(3):324-332. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9639075.

76. Geschwind MD, Skolasky RI, Royal WS, McArthur JC. The relative contributions of HAART and alpha-interferon for

therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol*. Aug 2001;7(4):353-357. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11517416.

77. Nath A, Venkataramana A, Reich DS, Cortese I, Major EO. Progression of progressive multifocal leukoencephalopathy despite treatment with beta-interferon. *Neurology*. Jan 10 2006;66(1):149-150. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16401874.
78. Przepiorka D, Jaeckle KA, Birdwell RR, et al. Successful treatment of progressive multifocal leukoencephalopathy with low-dose interleukin-2. *Bone Marrow Transplant*. Dec 1997;20(11):983-987. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9422479.
79. Buckanovich RJ, Liu G, Stricker C, et al. Nonmyeloablative allogeneic stem cell transplantation for refractory Hodgkin's lymphoma complicated by interleukin-2 responsive progressive multifocal leukoencephalopathy. *Ann Hematol*. Jul 2002;81(7):410-413. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12185517.
80. Kunschner L, Scott TF. Sustained recovery of progressive multifocal leukoencephalopathy after treatment with IL-2. *Neurology*. Nov 8 2005;65(9):1510. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16275856.
81. Vendrely A, Bienvenu B, Gasnault J, Thiebault JB, Salmon D, Gray F. Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy. *Acta Neuropathol (Berl)*. Apr 2005;109(4):449-455. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15739098.
82. Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology*. Apr 28 2009;72(17):1458-1464. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19129505.
83. Miralles P, Berenguer J, Lacruz C, et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after highly active antiretroviral therapy. *AIDS*. Sep 28 2001;15(14):1900-1902. Available at http://www.ncbi.nlm.nih.gov/pubmed/11579261.
84. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron RL. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. *Clin Infect Dis*. Nov 15 2002;35(10):1250-1257. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12410486.
85. Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment. *J Neurol Neurosurg Psychiatry*. Aug 2003;74(8):1142-1144. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12876257.
86. Di Giambenedetto S, Vago G, Pompucci A, et al. Fatal inflammatory AIDS-associated PML with high CD4 counts on HAART: a new clinical entity? *Neurology*. Dec 28 2004;63(12):2452-2453. Available at http://www.ncbi.nlm.nih.gov/pubmed/15623736.
87. Marzocchetti A, Di Giambenedetto S, Cingolani A, Ammassari A, Cauda R, De Luca A. Reduced rate of diagnostic positive detection of JC virus DNA in cerebrospinal fluid in cases of suspected progressive multifocal leukoencephalopathy in the era of potent antiretroviral therapy. *J Clin Microbiol*. Aug 2005;43(8):4175-4177. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16081969.
88. Khatri BO, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. *Neurology*. Feb 3 2009;72(5):402-409. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19188571.
89. Ransohoff RM. PML risk and natalizumab: more questions than answers. *Lancet Neurol*. Mar 2010;9(3):231-233. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20117056.
90. Martin-Blondel G, Cuzin L, Delobel P, et al. Is maraviroc beneficial in paradoxical progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome management? *AIDS*. Nov 27 2009;23(18):2545-2546. Available at http://www.ncbi.nlm.nih.gov/pubmed/19907215.